REMARKS: CLAIM REJECTION UNDER 35 U.S.C. § 103(a)

Claims 1-8 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement; and claims 9, 10, 12 and 13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Gidlund U.S. Patent No. 6,436,449 ("Gidlund"). Accordingly, Applicant respectfully submits the following.

Rejections Under 35 U.S.C. §112

Applicant respectfully submits that the phrase "less than 0.1 ml per kg of body weight of a patient" finds adequate support in the specification as filed and thus does not add new matter. The specification indicates that selective inhibition of COX-2 relative to COX-1 was observed in research and indicated that at a solution of 2.3 percent of *Morinda citrifolia* juice inhibited COX-2 by 60% while the inhibition of COX-1 was only 20 percent. Thus, the specification indicates that *Morinda citrifolia* juice shows selective COX-2 inhibition only when administered at very low dosages.

Specifically, the limitation of the maximum dosage of 0.1 ml per kg of body weight of a patient finds support in the specification at page 15, line 1 to page 15, line 7. The specification indicates that "biochemical assay results show that a concentration of 2.3 percent inhibition of COX-1 enzyme is four times less than inhibition of the COX-2 enzyme. Alternatively, this demonstrates COX-2 is inhibited to four times the extent as COX-1. Specifically, the results show that inhibition of COX-1 was 20 percent while inhibition of COX-2 was almost 60 percent. When the concentration was increased to 10 percent, the inhibition of COX-1 is shown to be approximately 83 percent while the inhibition of COX-2 is approximately 84 percent." Accordingly, the Applicant's originally filed specification supports "the surprising result that in

some circumstances less "*Morinda citrifolia* juice provides more [selective] inhibition..." Specification, page 15.

Applicant's disclosure shows that COX-2 selectivity is undermined by excessive, increased concentrations. Accordingly, the specification provides support for limiting the maximum dosage provided to a patient in a given period of time in a effort to maintain selective COX-2 inhibition. If a patient were given excessive doses of *Morinda citrifolia* in a given period of time the selective COX-2 inhibition of the administration would be undermined.

Rejections Under 35 U.S.C. §103

Applicant respectfully submits that Gidlund fails to teach the claim limitations cited in the present application because: 1) Gidlund does not teach administering low doses that produce **selective** COX-2 inhibition; and 2) Gidlund teaches a method for treating tinnitus not method for treating pain through **selective** COX-2 inhibition.

1. Gidlund Does Not Teach a Method for Reducing Pain By **Selective** COX-2 Inhibition.

The difference between treatment of pain and **selective** COX-2 inhibition is patentable. COX-2 expression is associated with pain and inflammation. COX-1 is a constitutively active enzyme responsible for maintaining the mucosal living of the stomach. When COX-2 is inhibited, pain is reduced. When COX-1 is inhibited, patients experience uncomfortable side effects, including gastric ulcers.

Compounds or formulations, which favorably influencing pain, do not have a reasonable probability for reducing pain by selective COX-2 inhibition. For example, a popular treatment of chronic pain and inflammation involves the use of non-steroidal anti-inflammatory drugs

(NSAIDs). NSAIDs inhibit both COX-2 and COX-1.While NSAIDs have been effective in reducing inflammation and pain, NSAIDs have a number of adverse side effects. The major side effects of NSAIDs are gastrointestinal related. In order to provide relief pain associated with COX-2 without inhibiting COX-1, drug companies have attempted to produce selective COX-2 inhibitors (e.g., VIOXX).

Applicant's claims contain limitations which require that the juice be administered in small dosages in order to limit undesired COX-1 inhibition. Applicants' disclosure demonstrates the importance and non-obviousness of administering the appropriate concentration of *Morinda citrifolia.* In particular, Applicants' experiments provide the non-obvious discovery that at some concentrations, selective COX-2 inhibition was achieved, and at other concentrations it was not. Specification, pg. 15. The Applicants indicated, "[t]he data suggests the surprising result that in some circumstances 'less' *Morinda citrifolia* juice provides 'more' inhibition selectivity." Specification, pg. 15. Applicants' disclosure shows that COX-2 selectivity is undermined by excessive, increased concentrations. Specification, pg. 15. It is only after the inherent COX-1 inhibiting qualities of *Morinda citrifolia* are limited by the methods of the present invention that selective COX-2 inhibition occurs.

2. Gidlund Teaches Administration of Excessive Dosages Which Do Not Produce COX-2 Inhibition.

It is desirable to produce a COX-2 inhibitor which is selective and allows the constitutively active COX-1 enzyme to maintain the mucosal lining in the stomach. These results suggest that limiting undesirable COX-1 inhibition by *Morinda citrifolia* juice may be accomplished only by appropriately limiting the concentration administered. Because Gidlund

teaches the administration of a quantity of juice that is higher than the amount necessary to achieve said **selective** COX-2 inhibition, the disclosure in Gidlund fails to read on the claims of the present invention.

The independent claims of the present invention include a limitation on the total amount of juice administered daily. Because Gidlund teaches that "the liquid extract from the *Morinda citrifolia* will be present in the medicament in the amount such as to provide a daily dosage of 0.1-2 ml, or 0.2-1 ml, e.g., 0.4-0.7 ml, per kg body weight of the patient," Gidlund fails to teach every claimed limitation of the present invention. Gidlund provides specific instructions in column 5, lines 16-19 that any liquid extract would be administered through patient at a minimum dosage of .1 ml per kg of body weight of a patient. Accordingly, a 70 kg patient would be administered 7 ml of liquid extract from *Morinda citrifolia* each day.

As described in example 1 of the specification of the present application, the dosaging of *Morinda citrifolia* juice is critical to achieving **selective** COX-2 inhibition. If an excessive amount of juice is administered, the selective COX-2 properties of the *Morinda citrifolia* juice are diminished. In particular, page 15 of the specification indicates that,

> Biochemical Assays show that a concentration of 2.31% produced an inhibition of COX- 2 which was 20%, while the inhibition of COX-1 was 10%, while the inhibition of COX- 2 was 60%. This is compared with the administration of 11% solution of *Morinda citrifolia* juice which produced an 83% inhibition of COX-1 and an 84% inhibition of COX-2. Accordingly, at greater concentrations, the selective COX-2 inhibition produced by the consumption of *Morinda citrifolia* products is limited.

Accordingly, COX-2 selective inhibition with *Morinda citrifolia* juice is sensitive or related to the concentration administered. Excessive concentration of *Morinda citrifolia* juice reduced the selective COX-2 inhibition properties of the administration. Accordingly, the administration disclosed by Gidlund which may be effective for inhibiting COX-2 **and** COX-1,